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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,652	08/07/2001	Ronald A. Laskey	620-161	9664

7590 09/22/2003

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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 09/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,652	LASKEY ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-90,101,102,104,105 and 107-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-90,101,102,104,105 and 107-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed June 25, 2003 (Paper No. 12) in response to the Office Action of February 25, 2003 is acknowledged and has been entered.

Claims 91-100, 103, and 106 were cancelled.

Claims 110-111 were added.

Claims 88-90, 101-102, 104-105, and 107-111 are pending and are currently under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Rejections/Objections:

Claim 88 is objected to for reciting "smaple", a misspelling in the claim.

Claim Rejections - 35 USC § 103

Claims 88-90, 101-102, 104-105, and 107-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Werness *et al.* Laboratory Investigation, Vol. 76, No.1, page 185A, March 1997, Abstract #1089 (cited in the Previous Office Action, Paper No. 11) in further view of WO/9716731 (Dunton *et al.* 09, May 1997)

Werness *et al.* teach a method of determining the presence or absence of dysplastic or neoplastic cells in a test sample containing cells from an individual (i.e., the samples were from primary human tumors and normal tissues) comprising contacting the test sample with an antibody directed against BM28/hMCM2 (see title) and determining the amount and or pattern of said antibody to the test sample whereby an increase in said amount and or a difference in said pattern if detected for the test sample compared with normal is indicative of presence of neoplastic cells in the test sample. Werness *et al.* teach that "tissue sections reacted with anti-BM28 gave strong nuclear signals in normal proliferating cells" and "tumors exhibited more intense positive staining of most nuclei"; the later reading **both** on wherein binding of the antibody to hMCM2 in the test sample is indicative of the presence of neoplastic cells (Claim 89) or wherein a difference in pattern of binding (i.e. more intense positive staining) of the antibody to said test sample compared with normal is indicative of the presence of neoplastic cells in said test sample (Claim 90). Also, since the tissues tested were from a multitude of primary human tumors and normal tissues, the art reads on the screening of a population of individuals (Claim 105).

Werness *et al.* does not specifically teach that the cellular samples were derived from fluid taken from the individual including such fluids as sputum, bronchio-alveolar lavage specimens, urine, breast duct fluid, brushings from the alimentary tract. Further Werness *et al.* does not specifically include analyzing cervical, fecal or urine cytology smears.

WO/9716731 teaches that Ki-67 is a "immunohistochemical" marker of dysplasia in the cervix and vulva (page 9). The authors further correlated the results of Ki-67 cervical cytology

staining with histopathologic diagnosis and found high sensitivity for the adjunctive test (page 21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the method of Werness *et al.* so as to include a test sample containing cells from an individual wherein the test sample comprises fluid specimens such as sputum, bronchio-alveolar lavage specimens, urine, breast duct fluid, brushings from the alimentary tract and or a test sample containing cells from cervical, fecal, or urine cytology smears. One would have been motivated to do so because Werness *et al.* successfully demonstrated that BM28/MCM2 is a diagnostic marker that is preferentially expressed in neoplastic cells versus normal proliferating cells. Extrapolating this knowledge to tumor cells derived from fluid samples is a mere variation from histological analysis of frozen tumor tissue cells as exemplified in the teaching of WO/9716731. Moreover, both references teach a nexus between Ki-67 and BM28/MCM2 in that both antigens are nuclear in location and are markers of cellular proliferation. Indeed, with 70/72 frozen tumor samples (97%) positively expressing BM28/MCM2, one of ordinary skill in the art would have a reasonable expectation of success that cellular samples from sputum, bronchio-alveolar lavage specimens, urine, breast duct fluid, brushings from the alimentary tract and or a test sample containing cells from cervical, fecal, or urine cytology smears would also be diagnostic of dysplasia or neoplasia.

Claims 88-90, 101-102, 104-105, and 107-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Todorov and Werness *et al.* (Laboratory Investigation, January 1998,

Vol. 78, No. 1, pages 73-78, IDS- also cited in the previous Office Action) in further view of WO/9716731 (Dunton *et al.* 09, May 1997).

Todorov *et al.* and Werness *et al.* teach as set forth except that the 72 tumor samples are specifically identified on Table 1, page 74. This includes tumors from breast, colorectal, kidney, lung, endometrium, stomach, pancreas, ovary, squamous cell, sarcoma, melanoma, and lymphoma samples.

Again, the authors do not specifically teach that the cellular samples were derived from fluid taken from the individual including such fluids as sputum, bronchio-alveolar lavage specimens, urine, breast duct fluid, brushings from the alimentary tract. Further Werness *et al.* does not specifically include analyzing cervical, fecal or urine cytology smears.

WO/9716731 teaches that Ki-67 is a "immunohistochemical" marker of dysplasia in the cervix and vulva (page 9). The authors further correlated the results of Ki-67 cervical cytology staining with histopathologic diagnosis and found high sensitivity for the adjunctive test (page 21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate their method so as to include a test sample containing cells from an individual wherein the test sample comprises fluid specimens such as sputum, bronchio-alveolar lavage specimens, urine, breast duct fluid, brushings from the alimentary tract and or a test sample containing cells from cervical, fecal, or urine cytology smears. One would have been motivated to do so because Werness *et al.* successfully demonstrated that BM-28/MCM2 is a diagnostic marker that is preferentially expressed in neoplastic cells versus normal proliferating cells. Extrapolating this knowledge to tumor cells derived from fluid samples is a mere variation

from histological analysis of frozen tumor tissue cells as exemplified in the teaching of WO/9716731. Moreover, both references teach a nexus between Ki-67 and BM28/MCM2 in that both antigens are nuclear in location and are markers of cellular proliferation. Indeed, with 70/72 frozen tumor samples (97%) positively expressing BM28/MCM2, one of ordinary skill in the art would have a reasonable expectation of success that cellular samples from sputum, bronchio-alveolar lavage specimens, urine, breast duct fluid, brushings from the alimentary tract and or a test sample containing cells from cervical, fecal, or urine cytology smears would also be diagnostic of dysplasia or neoplasia.

Applicant's primary arguments (Paper No. 12, page 8 and 10) are that the data from Werness and Todorov *et al.* are only from "histological" studies and do not refer to cytological samples. This argument has been considered but is not found persuasive. The fact that the prior art does not anticipate cytological analysis is not relevant because the above cited prior art is obvious over the claimed invention. Applicant further argue that there is no data to suggest that MCMs could enable detection of cells taken or released from the surface of an epithelial surface that can then be used diagnostically as in the presently claimed invention. This argument has been considered but is not found persuasive because the data teaches that cells can be taken from epithelial tumors and analyzed for their expression of BM28/MCM2.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
September 19, 2003